

REMARKS

The Examiner rejected claims 1-50 and 68. Claims 11, 12, 23, 25, 36, 37, 48, and 50 have been amended to more clearly describe the claimed invention and remove the language "selected from." Further, claims 12 and 37 have been amended to recite the word "species" and remove the abbreviation "sp." from the claims. The amendments to claims 11, 12, 23, 25, 36, 37, 48, and 50 are shown in the attached appendix. These amendments add no new matter. Claims 1-50 and 68 are under consideration.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 7, 10-12, 23, and 25-50 under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter. Office Action, page 2, section 4.

The Examiner rejected claims 10 and 35 as allegedly vague and indefinite for the language "is derived from." Office Action, page 3, section 4a. The Examiner points out that, "by and large, the language 'is derived from' is used to describe a chemical compound which has chemical modification." *Id.* Applicants agree that nucleic acids "derived from" a given source include those nucleic acids that are chemically modified. "During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification." Manual of Patent Examining Procedure (MPEP) §2173.05(a). It is clear that the Examiner understands that chemical modifications are within the scope of the nucleic acids used in the claims, and thus the claims are neither vague nor indefinite. Thus, the methods of claims 10 and 35 include embodiments where the nucleic acids from the sample are chemically modified.

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Applicants request reconsideration and withdrawal of the §112, second paragraph rejection.

The Examiner rejected claims 11-12 and 36-37 under 35 U.S.C. §112, second paragraph, as allegedly vague and indefinite for the language "selected from." *Id*, section 4b. Without acquiescing to the rejection, the claims have been amended to no longer recite the language "selected from." Thus, the rejection is moot. Applicants request reconsideration and withdrawal of the §112, second paragraph rejection.

The Examiner rejected claims 23, 25, 48, and 50 under 35 U.S.C. §112, second paragraph, as allegedly vague and indefinite for the language "selected from a group comprising." *Id*, section 4c. Without acquiescing to the rejection, the claims have been amended to no longer recite the language "selected from a group comprising." Thus the rejection is moot. Applicants request reconsideration and withdrawal of the §112, second paragraph rejection.

The Examiner rejected claims 7 and 31 under 35 U.S.C. §112, second paragraph, as allegedly vague and indefinite for the language "wherein the amplifying results in different amplification products." *Id*, section 4d. Specifically, the Examiner alleges that there is no antecedent basis for "the amplifying." Applicants respectfully point out that "the amplifying" is first recited in claims 1 and 26, from which claims 7 and 31 ultimately depend, claiming a method comprising "amplifying the at least one" Claim 1, lines 6-7, and claim 26, lines 9-10. There is only one amplifying step recited in each claim. Thus, "the amplifying" recited in claims 7 and 31 has proper antecedent basis.

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The Examiner rejected claims 26-50 under 35 U.S.C. §112, second paragraph, as allegedly vague and indefinite. Specifically, the Examiner alleges that it is unclear in which reaction composition the target polynucleotide is amplified, since there are two reaction compositions. *Id.*, section 4e. Claim 26 recites "amplifying the at least one target polynucleotide present in the reaction compositions" Further, both the first and second reaction compositions have amplification primers. Thus, one of ordinary skill in the art would clearly realize that the target polynucleotide, when present, is amplified in both the first and second reaction compositions.

The Examiner also alleges that it is unclear how one determines the presence of the at least one amplification product in both the first reaction composition and second reaction composition if the first reaction composition does not contain a fluorescent indicator. *Id.* Because the same sample is used in both the first and second reaction compositions, if the target polynucleotide is present in the second reaction composition, then one may deduce that the target polynucleotide is also present in the first composition reaction.

The Examiner further alleges that it is unclear how the sequence of the at least one amplification product of the first reaction composition is determined if the first reaction composition has no fluorescent indicator. *Id.* Claim 26, from which claims 27-50 ultimately depend, does not preclude a fluorescent indicator from being present in the first reaction composition. Neither does the claim require a fluorescent indicator in the first reaction composition. One of skill in the art would know several methods of determining the sequence of an amplification product. Several sequencing methods do not require the use of a fluorescent indicator in sequencing. For example, chain

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termination sequencing without fluorescent indicators is widely known and used in the art. See Sanger, et al., 1977, "DNA Sequencing with Chain-Terminating Inhibitors," *Proc. Nat Acad. Sci.* 74:5463-5467; and Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Third Ed. 2001, Chapter 12: DNA Sequencing. Applicants request reconsideration and withdrawal of the §112, second paragraph rejection.

The Examiner rejected claim 49 under 35 U.S.C. §112, second paragraph as allegedly vague and indefinite for the recitation of "a 5'-nuclease fluorescent indicator." The description of a 5'-nuclease fluorescent indicator, as described in the specification at page 9, paragraph no. 24, is quite clear and unambiguous. A non-limiting example of a 5'-nuclease fluorescent indicator, as described by the specification, is a short oligonucleotide possessing a fluorescent molecule at one end, and a molecule that quenches the fluorescent molecule's signal at the other end. When the oligonucleotide is intact, there is no fluorescent signal. When the oligonucleotide is broken, e.g., by the 5'-nuclease activity of DNA polymerase, then a fluorescent signal is generated. The Applicant's fail to understand exactly how the definition of 5'-nuclease fluorescent is unclear, and request that the Examiner more specifically explain what is unclear about the term or its definition. Applicants request reconsideration and withdrawal of the §112, second paragraph rejection.

Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-50 and 68 under 35 U.S.C. §103(a) as allegedly obvious. Office Action, page 4, section 5. Specifically, the Examiner rejected claims 1-25 and 68 as allegedly obvious over Pritham et al., 1998, *J. of Clinical Ligand Assay*,

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Vol. (4):404-412 ("Pritham"), in view of Johnston-Dow et al., U.S. Pat. No. 6,103,465 ("Johnston-Dow").

The Examiner asserted that Pritham does not disclose the sequencing method used to detect a specific target nucleic acid as recited in the limitations of claim 1. *Id*, page 5. Further the Examiner asserts that the "motivation is that the teachings of Pritham et al. indicate that fluorescent monitoring of PCR provides qualitative and quantitative information ... and the method of Johnston-Dow et al. applied the locus-specific nucleic acid amplification followed by sequence-specific detection of the amplified product for the DNA typing of HLA class I genes via DNA sequencing" *Id*, page 6.

However, the Examiner merely recited the qualities of the technologies disclosed in the references, but did not indicate where the references suggested a motivation to combine the references. "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves" MPEP §2143.01. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *Id*, citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). The Examiner has not shown that either Pritham or Johnston-Dow suggest:

"[a] method of determining the presence and sequence of at least one target polynucleotide in a sample comprising:
combining nucleic acid from the sample with at least one reaction composition comprising a fluorescent indicator and amplification primers specific to the at least one target polynucleotide;

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amplifying the at least one target polynucleotide present in the reaction composition using the amplification primers to obtain at least one amplification product;

irradiating the at least one amplification product such that the fluorescent indicator produces a fluorescent signal, wherein the intensity of the fluorescent signal is related to the quantity of the at least one amplification product;

monitoring the amplifying by detecting the fluorescent signal from the fluorescent indicator;

determining whether the at least one amplification product is present from the intensity of signal from the fluorescent indicator; and

determining the sequence of the at least one amplification product if the at least one amplification product is present."

Thus, the Examiner has shown no suggestion or motivation to combine Pritham and Johnston-Dow, and has not made a case of *prima facie* obviousness.

The Examiner also rejected claims 26-50 as allegedly obvious over Pritham in view of Johnston-Dow and Wittwer et al., U.S. Pat. No. 6,174,670 ("Wittwer"). Office Action, page 6, section 7.

As stated in the arguments above, the Examiner has shown no motivation or suggestion to combine the teachings of Pritham and Johnston-Dow. The disclosure of Wittwer does not remedy this defect.

Applicants request reconsideration and withdrawal of the §103(a) rejections.

CONCLUSION

Applicants assert that pending claims 1-50 and 68 are allowable and request a timely issuance of a Notice of Allowance. In the event the Examiner does not find the claims allowable, Applicants request that the Examiner contact the undersigned at (650) 849-6676 to set up an interview.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: December 5, 2002

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